PC50

The impact of exercise on performance of an arm flexion force-matching task

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Changes in corticospinal excitability following fatiguing exercise have been studied with transcranial stimulation techniques (Gandevia, 2001; Todd et al. 2003). Cortical and spinal excitability changes have been examined for their contributions to central mechanisms of fatigue. The production of a set level of force following fatigue requires an increase in voluntary drive and an associated increase in the perception of the effort. Using transcranial magnetic stimulation (TMS) we examined changes in corticospinal excitability and the performance of an arm flexion force-matching test up to 1 hour post-fatiguing exercise.

Ten healthy volunteers participated in the study (3 females, 7 right handed, mean age 31 yrs). One week prior to testing, subjects participated in 3 training sessions of a force-matching task. The task required accurate production of isometric force (40% of maximum voluntary contraction (MVC)) by forearm flexion with the elbow positioned at 90 deg on a table. The training involved production of the target force with and without (eyes closed) visual feedback of force levels. The force-matching test required 15 consecutive attempts at producing 40% MVC with eyes closed and the mean force and coefficient of variation was determined before and up to 1 hour post-exercise. TMS was applied over the left motor cortex to the site evoking maximal responses in the right side forearm flexors. Stimulation was administered using a 70 mm figure of eight coil (rapid MagStim, MagStim Co. UK) at stimulus intensity 120% of resting motor threshold. The motor-evoked potentials (MEPs) were recorded by standard surface electromyography from right m. biceps brachii and brachioradialis, and were monitored before and at regular intervals post exercise. The exercise consisted of rapid, repetitive full arm flexion- extension, administered on the first day without weights (for 3.5 min), or 2 days later, with a weight (40% of MVC) until exhaustion (< 3.5 min).

There was a significant (8%) reduction in MVC immediately after fatiguing exercise (t test, $p<0.01$). There was a small decrease in relaxed MEP amplitude following fatiguing exercise at post 5 min, which did not reach significance. The average force produced in the force-matching tests post fatiguing exercise was 10.5% higher than the force produced after the non-fatiguing exercise, and this difference was significant (repeated ANOVA, $p<0.02$). The coefficient of variation for fatiguing exercise (11%) was significantly higher than for non-fatiguing exercise (8%), (t test, $p<0.02$).

Our findings suggest that the perception of force may be altered by fatiguing exercise, so that more force is produced when subjects must complete a force-matching test. A possible interpretation is that afferent information following fatiguing exercise is impaired and could account for a change in the perception of effort.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

PC51

The effect of chronic electrical stimulation to forearm extensor muscles on cortical plasticity

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Chronic electrical stimulation is frequently used in neurorehabilitation [1]. Transcranial magnetic stimulation (TMS) studies have shown that there is short duration (<2hr) changes in motor cortical excitability following brief bouts of electrical stimulation (ES) of nerves and muscles [2]. This study examined changes in cortical motor excitability in normal subjects following 6 weeks of daily ES.

Five subjects (2 female, 1 left hand dominant, 25-55 years) underwent half hour daily sessions of ES to dominant side m. extensor carpi ulnaris (ECU) for 6 weeks. ES was delivered for 30 min in 10 sec trains of 20 Hz; 2-10 mA; ramping 5 sec rise and fall, delivered via surface electrodes and reinforced by concurrent volitional contraction. The non-dominant ECU received no exercise or treatment.

TMS stimuli were applied using a biphasic Magstim unilaterally to the hot spot for ECU of the left and right motor cortex. Motor evoked potentials (MEPs) were recorded from surface electrodes over ECU. Stimulus–MEP response curves for each side were obtained from average MEPS (n=5) in response to a series of stimulus intensities (30 to 100% maximal stimulus output) at 5% increments obtained before, at 3 weeks, and at 6 weeks of electrical stimulation. The nonlinear curves were fitted with Boltzmann function [3] using PC software (Sigmaplot 2000). The mean and S.D. for the stimulus-response curves are shown in Table 1. No significant differences between the parameters of the stimulus-response curves (repeated measures ANOVA) were obtained for either side. This suggests that in normals, the well known effects of ES, is similar to several weeks of resistance training [3] in not inducing long lasting reorganization of motor cortex, despite producing short term changes in cortical excitability. However, further work is needed to investigate plasticity at a spinal and cortical level following chronic electrical stimulation.

Table 1. The mean (n=5) curve fitting parameters for the control and ES side MEP responses from ECU are shown

		Control side			FES side		
		Pre	3 weeks	6 weeks	Pre	3 weeks	6 weeks
MEP_{max}	Mean	0.607	0.657	1.072	0.53	0.927	1.055
	S.D.	0.435	0.841	1.063	0.722	0.195	0.810
Slope ($K\%^{-1}$)	Mean	5.695	5.708	12.083	5.564	8.792	5.476
	S.D.	3.713	4.426	5.161	2.695	5.710	2.287
S_{50} (%)	Mean	69.172	67.668	77.996	63.005	69.435	65.979
	S.D.	15.503	16.693	7.724	6.797	4.393	8.898

$MEP_s = MEP_{max}/[1 + e^{(S_{50}-S)/k}]$ was used to fit the data, where MEP_s was the response amplitude for a given stimulus (S), MEP_{max} the response at maximum intensity, S the intensity, and S_{50} was the intensity at 50% maximum. The stimulus intensity units are a % of maximal magnetic stimulation output.

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PC52

Phase-dependent modulation of cutaneous reflexes during ankle extension and isometric contraction in humans

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Local cutaneous reflex has been suggested to promote placing and stability during rhythmic and locomotor activity (Zehr & Stein, 1999). Recently a role for cutaneous receptors in functional recovery after spinal cord injury has been identified in animal studies (Bouyer & Rossignol, 2003), and has been suggested to represent an important neural mechanism promoting rehabilitation (Pearson, 2003). The objective of this study was to identify the exact role of local cutaneous stimulation (plantar versus heel) on short and long-latency tibialis anterior (TA) and gastrocnemius medialis (GM) reflex activity during controlled rhythmic motor activity in healthy volunteers and in spinal cord injury (SCI) patients, to facilitate the development of future neurosensory rehabilitatory techniques.

Healthy volunteers and SCI patients were instructed to perform ten ramp and hold contractions of the triceps surae in the dominant leg to reach 50% of maximal voluntary contraction (MVC), while electrically evoked modular cutaneous reflex electromyographic activity was measured at rest, during ankle extension and isometric contraction. Reflex activity was full wave rectified, after DC offset removal and the early (50-100 ms), late (100-200 ms) and total (50-200 ms) response was integrated (Spike2, Version 5.11, CED Ltd). Background EMG activity was subtracted from the reflex activity obtained during R, AE and IC. Integrated data was normalized: (reflex integral during AE/IC trial)/(reflex integral at R)-1 so that mean reflex activity during R represented as '0'. Statistical analysis was performed using the Mann-Whitney U test (SigmaStat, Version 3.1, Jandel Scientific).

In general the total cutaneous reflex plantar-TA activity was significantly inhibited during ankle extension (-0.96±0.37; $p<0.05$) and isometric contraction (-1.06±0.32; $p<0.01$) at 50% MVC compared to the 'rest' phase (0.0±0.35). Analysis of the early (50-100 ms) plantar-TA and heel-GM reflex activity also indicated significant inhibition during both ankle extension and isometric contraction. During isometric extension the inhibition of the early plantar-GM reflex (-1.61±0.19) was significantly greater than the heel-GM reflex (0.82±0.15). Data from SCI patients will be presented as case reports.

Measurement of phase-dependent cutaneous reflex modulation during ramp and hold rhythmic movement is a powerful and sensitive diagnostic technique for measuring sensorimotor function and will be instrumental in evaluating sensory neurorehabilitatory techniques in the future.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

PC53

Assessment of connections in the rat thoracic spinal cord suitable for testing in experimental spinal cord repair

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Studies of regeneration in experimental spinal cord repair rarely identify whether the regenerating axons make appropriate connections. Here we aim to characterize specific connections in normal rats, for later comparisons with regenerating axons. Respiratory axons are used to allow definition of functional specificity. Thoracic motoneurones are used as targets so that connections can be readily identified. Importantly, these motoneurones may be contacted by regenerating axons with a minimal regeneration distance after a spinal cord transection.

Experiments were made on vagotomized rats anaesthetized with ketamine plus xylazine (induced, I.P., 100mg/kg, 10 mg/kg, respectively, then I.V. as required), or urethane (1.4g/kg, I.P.) or halothane (induced 5%, then as required), or decerebrated under ketamine plus xylazine (as above). Neuromuscular blockade (pancuronium bromide at 0.3mg/hr I.V.) and artificial ventilation were used, with CO_2 added to the inspired gas to enhance the respiratory drive. Adequacy of anaesthesia was assessed by observations of blood pressure and respiratory patterns following noxious paw pinches. Extracellular recordings were made from single expiratory bulbospinal neurones (EBSNs) in the caudal medulla, antidromically identified from T11. Connections from EBSNs to motoneurones were sought either by cross-correlation between EBSN discharges and efferent discharges in contralateral intercostal nerves (T6-T10), or by spike-triggered averaging (STA) to contralateral thoracic motoneurones (intracellular recording, T9-T10).

Expiratory discharges occurred in both internal and external intercostal nerves, extending observations of Tian & Duffin (1996). Under anaesthesia, such discharges occurred only when the anaesthesia was light, and were often weak or intermittent. Correlation results to date derive from decerebrate preparations with strong expiratory discharges. Monosynaptic connections have consistently been shown to internal intercostal nerve motoneurones (7/14 EBSNs, 5 animals), using criteria from Kirkwood (1995) related to latencies and durations of peaks in the

cross correlation histograms. Monosynaptic connections were not detected to external intercostal nerve motoneurones, but in one animal several EBSNs gave correlation peaks indicative of disynaptic connections and, in another animal, troughs were seen, indicative of di- or trisynaptic inhibition. STA has so far revealed no EPSPs in expiratory internal intercostal nerve motoneurones under ketamine/xylazine anaesthesia (12 pairs tested, 3 animals).

Direct, and possibly also specific indirect connections from EBSNs to thoracic motoneurones are therefore normally present in the rat, allowing comparison with newly formed connections of regenerating EBSN axons.

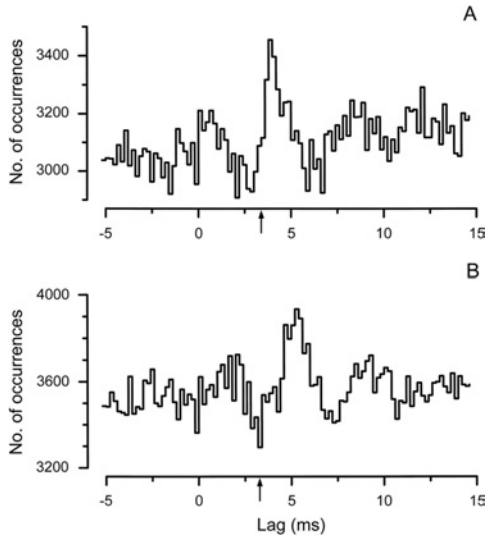

Figure 1. Cross-correlations for an EBSN and internal (A) and external (B) intercostal nerves (arrows, monosynaptic latencies).

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PC54

The contribution of extension to withdrawal reflexes in the anaesthetized rabbit measured by movement analysis

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According to Sherrington (1910), hind limb withdrawal to noxious stimulation of the skin is considered to be a monolithic flexion reflex such that wherever the stimulus is applied the same response is observed, namely flexion at the hip, knee and ankle. Contrary to this view, an accumulation of evidence suggests that extensors are also involved in the withdrawal response with the actual muscles recruited being dependent on the location of the noxious stimulus (Clarke et al. 1989; Schouenborg & Kalliomaki, 1990). The conclusions of these studies have been based on findings using electrophysiological recording in hind limb muscles rather than measurement of actual movements, therefore the aim of the present study was to use an image analysis system to address this issue.

Experiments were performed on 14 rabbits lightly anaesthetized by a continuous i.v. infusion of Saffan (between 4 and 30 mg kg^{-1} h^{-1}). Reflex responses were evoked by mechanical pinch of the skin using toothed forceps fitted with a pressure transducer (mean force 1.4 ± 0.1 kg for 1.6 ± 0.2 s). Stimuli were applied to eight locations on the hind limb but only data from pinching the left heel or toes are reported here. Reflex movements of the left hind limb were measured using a CODAmotion movement analysis system which enabled angles at the hip, knee and ankle joints to be calculated via detection of strategically located infrared emitters.

The first response to mechanical pinch at the heel was extension of the ankle at a latency of 245 ± 44 ms (mean ± S.E.M.). This was followed by significantly later flexion at the knee and hip (348 ± 51 and 352 ± 49 ms, respectively; repeated measures ANOVA, $p = 0.01$). The mean angle change for extension at the ankle was 6 ± 1.5 deg and values for flexion at the knee and hip were 12 ± 1.1 and 9.8 ± 1.3 deg, respectively. In contrast, there was no significant difference in the latency of the ankle, knee and hip responses to noxious mechanical stimulation of the toes (559 ± 100, 530 ± 89 and 561 ± 89 ms, respectively; repeated measures ANOVA, $p = 0.4$) but these values were significantly longer compared to heel pinch (paired t tests, $p < 0.05$). Following toe pinch, the mean angle change for extension at the ankle was 7.8 ± 2.2 deg, whereas flexion at the knee and hip joints was by 16.1 ± 2.2 and 7.0 ± 0.9 deg, respectively. Mean angle changes induced by pinch at the heel and toes were not significantly different (paired t tests, $p > 0.05$).

By measuring actual movements, these data show that extension of the ipsilateral hind limb is an important part of the withdrawal response to noxious stimulation. Furthermore, the contribution of extension to reflex withdrawal is dependent upon the site of the stimulus and the joint studied.

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PC55

The role of the cerebellum in auditory paced finger tapping

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Rhythmicity is an essential temporal component of movement strictly embedded in many motor control functions. The tim-

ing process appears to be coded in a distributed network of brain regions depending upon task specifics. The present study attends to investigate by transcranial magnetic stimulation (TMS) the role of different neural structures in the finger tapping test at different conditions. Nine healthy right-handed subjects participated in the main experiment. rTMS (10 min. 90% of resting motor threshold) was applied over the right and left cerebellar hemisphere (RCH, LCH) and ipsilateral primary motor area (M1) in three different sessions. In each session subjects were asked to tap on the surface of a force transducer with their right index finger in synchronization with an auditory cue at 0.5, 1 and 2 Hz, before rTMS, after rTMS and 15 min after rTMS. The ANOVA show a significant impairment in the variability in the intertap intervals (ITI) ($P<0.02$) and in the mean accuracy at 2 Hz ($P<0.03$) after the rTMS over the RCH. This effect is present only with auditory cue and not with visual cue and not when the task is autoself-generated (continuation task). In control experiments, rTMS over the contralateral premotor area showed impairment in the variability of ITI at 2 Hz ($P>0.04$) without any effect onthe SMA. These results support the hypothesis of neural network for timing process specific to the characteristics of the task such as the presence and nature of the cue and the duration of the range time.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

PC56

Corticospinal and intracortical excitability acutely and longitudinally after hemispheric stroke

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Ischaemic stroke commonly causes hand weakness followed by a variable recovery of function. Transcranial Magnetic Stimulation (TMS) has previously uncovered abnormalities in both corticospinal (Catano et al. 1996; Traversa et al. 2000) and intracortical (Liepert et al. 2000; Manganotti et al. 2002) excitability in both hemispheres after stroke. Although the first month sees the greatest functional gains there is little longitudinal data addressing physiological changes in this period. Moreover, although some physiological measures have been related to function the changes in this relationship with time are unknown. We set out to investigate the evolution of corticospinal and intracortical excitability and to relate these to hand function.

Ten patients with first ever ischaemic stroke were studied frequently during the first month using TMS and clinical assessments – patients were followed up at 3 and 6 months.

In the affected hemisphere (AH) active motor thresholds were raised and MEP recruitment curve (RC) gradients were reduced during the first month (unpaired t tests, P=0.004 and 0.009, respectively). Active thresholds improved with time (1st to 3 months, P=0.046) but remained higher than normal at 6 months. Gradients in the UH were raised initially compared to the AH (paired t test, P=0.001) and showed a trend reduction from the 1st to 3 months (P=0.051) – UH gradients in the 1st month were more raised after subcortical than cortical stroke (P=0.003). Short interval (SICI) and long interval (LICI) intracortical inhibition were abnormally weak in the AH (P=0.032 and 0.048, respectively) and remained unchanged. In the AH, SICI was weaker after cortical than subcortical stroke (P=0.007).

Correlations between measures of hand function and corticospinal excitability in the AH were strong during the acute period (active thresholds r=-0.67; RC gradients r=0.77) but weaker at 3 months (r=-0.47 and r=0.54, respectively). By contrast, similar correlations with measures of intracortical excitability were weak initially (UH SICI r=-0.55; UH LICI r=-0.48) and strong at 3 months (r=-0.69 and -0.74, respectively). We conclude that while patients rely initially upon what remains of the original corticospinal projection, time and motor practice allow networks in non-primary areas to become organised – intracortical disinhibition may allow continued access to these networks in the subacute period. The correlations between intracortical excitability and functional measures became weak by 6 months. This period coincides with the proliferation of perilesional terminal fields described after ischaemic infarcts in monkeys (Dancause et al. 2005). Thus structural changes between 3 and 6 months may reduce reliance on disinhibition for continued access to alternative motor networks. The data suggest that recovery from stroke is a dynamic and staged process.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

PC57

Indirect wave facilitation of transcallosal pathways in humans

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Transcallosal inhibition can be studied in humans using transcranial magnetic stimulation (TMS) using two protocols: ipsilateral silent period (ISP) and interhemispheric inhibition (IHI). Recently, a paired-pulse protocol that normally produces short-interval intracortical inhibition (SICI) on corticospinal output was also shown to reduce the transcallosal inhibition as measured by ISP (Trompetto *et al.* 2004). This shows that transcallosal neurons are modulated by inhibitory interneurons in a similar way to corticospinal neurons.

Tokimura *et al.* in 1996 described that paired pulses of equal intensities produce a 3-phase pattern of facilitation of the corticospinal pathway that is believed to be due to facilitatory indirect 'I' wave interaction. The aim of our study is to identify if a similar excitatory modulation of transcallosal neurons exists using ISP and IHI.

Motor evoked potentials were recorded from both first dorsal interossei (FDI) muscles in 10 healthy subjects. For the ISP protocol, 2 stimuli of equal intensity were delivered at different interstimulus intervals (ISI) to the left primary motor area (M1) while the subjects were activating the left FDI. The ISIs used were 1.3ms, 1.5ms, 2.0ms, 2.5ms, 3.0ms, 3.3ms, 3.5ms and 4.3ms; and the intensity of stimulation was set at the threshold for evoking ISP. For the IHI protocol, subjects were at rest and 2 conditioning stimuli (separated by the same ISIs as above) were applied to the left M1 with a test stimulus to right M1 40ms later. The intensities of the conditioning stimuli were equal and set at the threshold for IHI.

For both the protocols, we found that the MEP in the right FDI was facilitated at 1.5ms and 3.0ms ($p<0.05$). ISP area was also facilitated at the same ISI in the left FDI ($p<0.05$). IHI from left-to-right M1 was enhanced at these ISI ($p<0.05$). The increase of ISP area and the degree of IHI were both correlated with the degree of I-wave facilitation in the other hemisphere ($p<0.05$). This is compatible with the idea that neural circuits that generate I-wave inputs to corticospinal neurons in cortical layer V also exist for transcallosal pyramidal neurons in layer III.

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

PC59

Patterns of abnormal cerebral metabolism in late-infantile PANK2 mutation-positive neurodegeneration with brain iron accumulation type 1 (NBIA 1) (Hallervorden Spatz Disease) measured using 18F-fluoro-deoxyglucose positron emission tomography and statistical parametric mapping

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Neurodegeneration with brain iron accumulation 1 (NBIA 1: formerly known as Hallervorden-Spatz disease) comprises a rare group of autosomal recessive extrapyramidal movement disorders accompanied by iron accumulation in the globus pallidus and nigrostriatal pathways and mutations in the pantothenate kinase (PANK2) gene [1,2]. Here, we demonstrate the cerebral functional metabolic correlates in patients with NBIA1, assessed prior to deep-brain stimulation (DBS) [2].

Brain glucose metabolism was measured using 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) using high-sensitivity 3D acquisition in five children aged 4, 9, 10, 13 & 14 years old with late infantile PANK2 disease. Regional differences in brain glucose uptake were analysed by statistical parametric mapping using SPM2 software (www.fil.ion.ac.uk) to compare subject scans with a normative database of 20 subjects aged 40-60 years.

All the PANK2-positive PET-CT scans were considered normal on routine clinical inspection. Between groups SPM2 comparison showed significant cerebral hypometabolism within bilateral globus pallidus, cerebral peduncles, occipital cortex, cerebellar vermis, and pons ($p < 0.001$). The statistical parametric maps of hypometabolism for the group of five cases is shown superimposed on an average of 156 MRIs in MNI (Montreal Neurological Institute) space in sagittal (a), coronal (b) and axial (c) planes. Late infantile PANK2-positive NBIA1 is associated with decreased metabolism within bilateral visual cortex, globus pallidi, cerebral peduncles, dorsal pons and cerebellar vermis. Although further comparisons with age-matched paediatric controls are required, hypoperfusion of the head of the right caudate nucleus, pons, cerebellar vermis have been previously reported in one case with PANK2 disease [3]. Hypometabolism extending beyond the pallidal-substantia-nigra abnormalities identified on MRI could reflect functional or structural deficits. If functional, they may provide a measure of response to DBS.

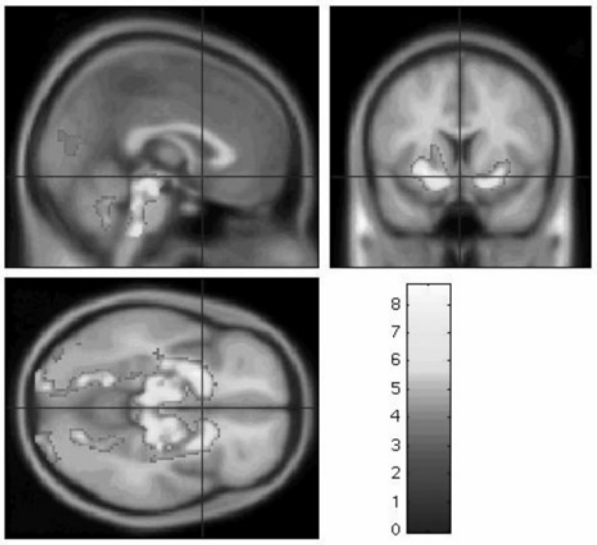

Figure 1

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Where applicable, the authors confirm that the experiments described here conform with the Physiological Society ethical requirements.

PC61

Estimation of post-synaptic potentials in motoneurons evoked by cutaneous stimulation in man

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The mechanisms underlying the triggering of muscle spasms from non-noxious sensory stimulation after spinal cord injury (SCI) remain unknown. Following SCI in rats, long-lasting reflexes (spasms) can be triggered from weak, single shock cutaneous stimulation due to the activation of persistent inward calcium currents (PICs) in the motoneuron (Li & Bennett, 2003). Such cutaneous stimulation produces NMDA-mediated excitatory post-synaptic potentials (EPSPs) in the motoneuron that are very long-lasting, ranging from 0.5-2s. These long EPSPs are able to recruit the slowly activating PIC, which requires depolarizations of 200ms or more. The purpose of this on-going study is to examine if, in man, EPSPs from non-noxious, spasm-triggering sensory inputs are similarly prolonged after spinal cord injury compared to non-injured controls to determine if they more readily activate motoneuron PICs.

To estimate PSPs in man, the technique of peristimulus frequencygrams (PSFs) was used where the mean instantaneous firing rate relative to a stimulus is plotted. Changes in firing rate from background are thought to reflect changes in the underlying membrane potential and circumvent count-related errors associated with other measures such as the peristimulus time histogram (Turker & Powers, 2005). In non-injured controls, single shock stimulation to the medial arch of the foot, a stimulation that readily triggers muscle spasms in patients with SCI, was tested in 3 non-injured control subjects. The duration of the estimated PSP (recorded from the tibialis anterior muscle) produced from a non-noxious stimulation was surprisingly long, ~281±30ms (n=9 units, 2 units from 2 subjects and 3 units from 1 subject), as determined by the corner points of the CUSUM of the PSF (Ellaway, 1978). To determine if these prolonged increases in firing rate above background were due to a long PSP and not a result of history-dependent effects of tonic cell discharge (see Turker & Powers, 2005), direct intracellular recordings of motoneurons were made from the sacral spinal cord of an adult rat. Here, current injections that produced PSPs similar to that predicted from the PSF in humans were directly compared. Intracellular recordings revealed that for long EPSPs (>200 ms), with a slowly falling membrane potential following the initial depolarisation, the PSF profile faithfully followed the membrane voltage trajectory. Synchronization and history dependent effects on motoneuron discharge, which give a false representation of the PSP, only became a problem in cases where motoneurons had weak sodium-mediated PICs, currents that have been shown to be critical in motoneuorn firing (Lee et al. 2003; Harvey et al. 2005).

In summary, we have shown that even in non-injured controls, very long estimated PSPs (~281ms) can be produced from single shock cutaneous stimulation as reflected in PSF profiles from motor unit recordings. The next step is to investigate effects of chronic SCI on these PSPs and its role in triggering muscle spasms.

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